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on Left Ventricular Function in Patients with Ischaemic Heart Disease
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Abstract

Purpose. This study sought to determine the effects of a supervised cardiac rehabilitation exercise programme on left ventricular function in patients with ischaemic heart disease and any degree of left ventricular systolic dysfunction.

Subjects. At the time of this interim report twelve male subjects (median age 59 years, interquartile range 56 – 67.75) and five female subjects (median age 70 years, interquartile range 55 - 72) have been recruited to the study. Eight patients are in the exercise group and nine in the control group. Eventually twenty patients will be required in each group for statistical significance.

Methods. This is a repeated measures design. Echocardiographic measurements of left ventricular function were taken at the time of recruitment and repeated after a 6 week programme of exercise. Control group measurements were repeated after a similar period of usual care without exercise.

Results. Both groups show an improvement in ejection fraction on repeated measurement but only the exercise group reaches statistical significance (median EF pre 43.0%, median EF post 58.6%, $p=0.025$). Neither group shows any significant difference in measures of diastolic function.

Conclusion. An exercise based cardiac rehabilitation programme has a positive effect on left ventricular ejection fraction in patients with ischaemic heart disease and any degree of left ventricular systolic dysfunction. There is no effect on diastolic function. It remains to be seen if these findings are maintained at the end of recruitment.

This work is original, contains between 12-16000 words and has not been submitted previously in support of a degree qualification or other course

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Introduction

Exercise based cardiac rehabilitation has been available in the United Kingdom (UK) since the late 1960's. Initially resources were very limited, forcing rehabilitation staff to target their services at a narrow patient group, mainly white, middle class, male survivors of myocardial infarction (O'Connor et al, 1989). However, a variety of factors have led to the increased provision of such services. These include the availability of British Heart Foundation (BHF) start-up grants (from 1989), the increasing credibility given to cardiac rehabilitation as an effective intervention which reduces mortality and morbidity, and Government guidelines recommending the provision of cardiac rehabilitation (Department of Health, 2000). Today there are more than 350 cardiac rehabilitation centres throughout the UK who are providing services to a wide range of patient groups.

This in turn had led to the publication of a large volume of research on the beneficial effects of exercise based cardiac rehabilitation in a variety of patient groups. One group of patients who are now subject to an increasing amount of research is those with heart failure.

Heart failure has a number of causes including cardiomyopathies, coronary heart disease, valvular heart disease and hypertension. It is characterized by left ventricular dysfunction to a greater or lesser degree and is often accompanied by global or regional dilation of the ventricle (ventricular remodeling). This dysfunction may be either systolic dysfunction, diastolic dysfunction or both. Patients presenting with

symptoms of heart failure but with preserved systolic function are often presumed to have diastolic dysfunction even when diastolic function has not been assessed (Thomas, Fox, Coats, & Sutton, 2004). However, as symptoms of heart failure can be due to non-cardiac causes, e.g. pulmonary disease, obesity, anaemia and fluid overload secondary to renal impairment, it is important that a formal assessment of diastolic function is made.

Echocardiography is the most practical method of assessing cardiac function (Task Force for the diagnosis and treatment of chronic heart failure, European Society of Cardiology, 2001). Galasko, Basu, Lahiri & Senior (2004) have recently proved that echocardiography, using Simpson's method to measure left ventricular ejection fraction, is a valid tool for the assessment of left ventricular systolic function in survivors of myocardial infarction. Simpson's method involves tracing the outline of the left ventricle on an apical four chamber image. This is done at the end of diastole, when the ventricle is at its maximum volume, and at the end of systole, when it is at its minimum volume. Computer software is then used to divide the left ventricular cavity into a number of slices of known thickness and diameter to determine the volume at end diastole and end systole and therefore calculate the percentage change in volume, i.e. the ejection fraction.

Other echocardiographic techniques can also be used to determine left ventricular systolic function but these are not as accurate. Ejection fraction can be measured in Motion or M-mode, which measures the diameter of the left ventricular chamber at

end diastole and end systole at the level of the mitral valve leaflet tips in the parasternal long axis view. These measurements are then converted to estimates of volume. However this method does not account for regional ventricular wall motion abnormalities and patients with poor left ventricular function can have normal M-mode measurements. Another commonly reported measure is fractional shortening, which is the percentage change in left ventricular internal dimensions between systole and diastole. However, this again does not take into account regional wall motion abnormalities and can produce an erroneous impression, especially in patients with regional myocardial damage (myocardial infarction).

It should be remembered that all the above are 2-dimensional measurements of a 3-dimensional function and are therefore liable to error, especially in patients with regional myocardial damage. However, as stated above, Simpson's method has been shown to be a valid and reliable method of measuring left ventricular ejection fraction (Galasko, Basu, Lahiri & Senior, 2004).

Assessment of diastolic function is more complex as a number of variables need to be measured, including isovolumetric relaxation time and several aspects of trans-mitral flow patterns (the flow of blood from the left atrium through the mitral valve into the left ventricle). However, careful interpretation of these measurements gives an accurate assessment of diastolic function (Oh et al, 1997).

It is important to consider the impact of left ventricular dysfunction on both quality of life and mortality risk. Left ventricular dysfunction can significantly impair exercise capacity and in so doing reduce quality of life. It has been known for many years that the severity of left ventricular systolic dysfunction correlates poorly with exercise capacity and quality of life. Bengtsson, Litchfield & Marcus (1980) treadmill tested 26 patients with an ejection fraction of 30% or less and found that half of them had a normal exercise capacity. Left ventricular diastolic function however, has been shown to be an important determinant of exercise capacity in a variety of patient groups, including those with previous myocardial infarction (Miyashita et al, 2001; Sakate et al 2001), those with dilated cardiomyopathy (Parthenakis et al, 2000) and in patients with type II diabetes without coronary disease (Poirier et al, 2000).

Mortality from heart failure, although high, is difficult to determine accurately, as guidance on the completion of death certificates states that heart failure is a mode of death rather than a cause, so many heart failure deaths will be recorded as the underlying cause of the heart failure, such as coronary heart disease (British Heart Foundation, 2002). Data from one population based study of patients newly diagnosed with heart failure demonstrated a 38% 1-year mortality rate (Cowie et al, 2000). Solomon et al (2005) examined the relationship between the left ventricular ejection fraction and all cause mortality in 7599 patients with heart failure. They found that the hazard ratio for all cause mortality increased by 39% for every 10% reduction in ejection fraction below 45% (hazard ratio 1.39, 95%CI 1.32-1.46).

Weir, McMurray & Velazquez (2006) recently published a review of the evidence for the prognostic significance of heart failure and left ventricular systolic dysfunction complicating acute myocardial infarction. They found consistent evidence from a large number of studies that heart failure increased both early (in-hospital) and 1-year mortality.

This high rate of morbidity and mortality has driven a great deal of research which has led to a number of advances in the pharmacological management of heart failure, notably the use of beta-blockers, angiotensin converting enzyme inhibitors and spironolactone. However, it is also important to consider non-pharmacological methods of heart failure management, such as exercise therapy.

Increasingly the management of heart failure patients is undertaken by specialist heart failure clinics or nurse led services. Such services have proved effective in improving quality of life and reducing hospital readmission rates (Blue et al, 2001). These services concentrate on optimizing pharmacological management and lifestyle interventions with the goal of reducing symptoms and improving functional status. Although cardiac rehabilitation centres traditionally have different goals for their patient groups (risk reduction and return to previous physical condition) combining these two services would allow exercise training for heart failure patients without the need for duplication of services and personnel (Caldwell & Dracup, 2001). This would require the development of specific heart failure rehabilitation programmes, but promises to further improve the management of heart failure patients in a cost-

effective manner. In order to develop such programmes a detailed understanding of the effects of exercise on cardiovascular function is necessary so that exercise programmes can have a sound scientific basis.

Summary of Existing Research

The effects of exercise on left ventricular function have been researched by a number of authors (summarized below). Exercise has been found to be both safe and beneficial in patients with heart failure (Giannuzzi, Temporelli, Corrà & Travazzi, 2003). However, the majority of research has been on systolic function and has been conducted in patients with dysfunction related to cardiomyopathies, or in normal subjects to examine the effects of ageing or life-long exercise on left ventricular function. There is relatively little research in patients with dysfunction from an ischaemic cause (coronary heart disease or myocardial infarction). Diastolic dysfunction is also under-researched and the majority of the available research has been conducted into the effects of long term endurance training and gives little indication of the effects of a relatively short-term programme of exercise, such as that used in most cardiac rehabilitation programmes.

Heart failure or left ventricular dysfunction is a common complication of myocardial infarction. Velazquez et al (2004) studied 5573 consecutive myocardial infarction patients at 84 hospitals in 9 countries from 1999 to 2001. They found that 42% had

heart failure or left ventricular systolic dysfunction during hospitalization. This was a very large international study and the results are likely to be generalizable to the majority of UK patients suffering myocardial infarction.

In healthy subjects left ventricular diastolic function tends to decrease with age.

Using validated echocardiographic techniques, Fischer et al (2003) found that in an age-stratified (25-75 years) European sample of the general population the incidence of diastolic dysfunction was 11.1%, and was more prevalent in older age groups (2.8% in those aged 25-35 years and 15.8% in those aged 65-75 years, $p < 0.01$).

However, age was not the only predictor of diastolic dysfunction. Arterial hypertension, coronary disease and left ventricular hypertrophy were also independent predictors, but in the absence of these factors diastolic abnormalities and diastolic dysfunction were rare even in the over 50's. High body mass index, high fat mass and diabetes were also associated with diastolic dysfunction. The authors speculated that diastolic heart failure may be prevented by improved implementation of measures directed against these predisposing factors or conditions.

That diastolic dysfunction is an inevitable consequence of ageing was also challenged by Arbab-Zadeh et al (2004). In this small scale study 12 healthy sedentary seniors (age 69.8 \pm 3 years), 12 Master athletes (age 67.8 \pm 3 years) and 14 young sedentary control subjects (age 28.9 \pm 5 years) underwent a variety of investigations to assess their left ventricular compliance (a measure of diastolic function). They found that there was substantially decreased left ventricular compliance in the healthy

but sedentary seniors compared to the young controls, but the data for the Master athletes closely matched that of the young controls. This suggests that long-term endurance training preserves left ventricular compliance with aging.

Their findings are supported by a previous study by Palka, Lange & Nihoyannopoulos (1999). In a study of 89 athletes (age 18-64, mean 37 years) and 105 age matched sedentary controls, left ventricular function was assessed by standard echocardiographic techniques. Compared with controls the athletes had significantly more rapid early ventricular filling (i.e. better diastolic function), and the age-related decline in diastolic function was significantly less pronounced.

However, it is important to note that in the study by Arbab-Zadeh et al (2004) the sedentary seniors compared to the master athletes weighed more ($73.3 \pm 10.6\text{Kg}$ v $64.6 \pm 13.5\text{Kg}$), had a higher average body mass index (25.8 v 22.3) and a higher body fat percentage (28.7 ± 7.2 v 17.6 ± 5.8). Although the sedentary seniors are by no means obese their body fat percentage is high and, considering the evidence from Fischer et al (2003), this must call into question whether preservation of diastolic function is due to habitual exercise or lack of predisposing factors for diastolic functional decline. Figures for the study by Palka, Lange & Nihoyannopoulos (1999) are not given.

These studies contradict a study of similar design which found that regular endurance training did not consistently modulate the changes in left ventricular diastolic

function commonly seen in physiological aging (Gates, Tanaka, Graves & Seals, 2003). Furthermore, in another similar study, Baldi et al (2003) claim that not only did long term endurance training not preserve left ventricular diastolic function, but one measure of diastolic function (mitral A wave flow velocity) was worse in trained compared to untrained older men. However, this single parameter does not reflect the overall picture of diastolic function, and this study serves to indicate some of the complexities of assessing diastolic function with a variety of echocardiographic parameters.

It is important to note that in both these studies (Gates, Tanaka, Graves & Seals, 2003; Baldi et al, 2003) the older endurance trained subjects had lower body mass index and body fat percentage, and in the study by Baldi et al (2003) the endurance trained subjects had a significantly lower systolic blood pressure than the older sedentary subjects. Yet despite this lack of predisposing factors and regular exercise neither study was able to demonstrate preservation of diastolic function.

The above studies provide conflicting evidence about the effects of long term endurance training on left ventricular diastolic function, but the effects of shorter training programmes have also been investigated.

Levy, Cerqueira, Abrass, Schwartz & Stratton (1993) investigated the effects of a 6-month endurance exercise programme on diastolic filling parameters in 14 older (age 60-82 years) and 17 younger (age 24-32 years) healthy males. As would be expected,

prior to training the older men had reduced early diastolic filling compared to the younger men. Endurance exercise training enhanced early diastolic filling in both the young and the older subjects indicating improved diastolic function. Unfortunately figures for pre and post training weight, body mass index and body fat percentage are not given, although the authors do note a small decrease in body surface area post training in the older group due to a small weight loss. A 6 month training period would certainly be enough to produce significant differences in body composition which, according to the data from Fischer et al (2003), may have had a beneficial effect on diastolic function.

Petrella, Cunningham & Paterson (1997) investigated the effects of a short-term (5 day) high intensity exercise programme in healthy sedentary older men (n=5) and women (n=2) (age 68+/-4 years). Echocardiographic variables were measured before training, after training and after 21 days of detraining. Training consisted of 60 minutes of high intensity cycling per day. Post-training there were significant improvements in measures of diastolic function, which returned to baseline after 21 days of detraining. Despite the small scale of this study statistical significance was reached. In a short 5-day training period there is little likelihood of significant changes in body composition, and indeed there was no significant change in weight. This study therefore provides more convincing evidence that the beneficial changes in diastolic function seen post-training were due to the effects of exercise, especially as they returned to baseline after a period of detraining, during which there was no weight gain.

These findings were in contrast to a study published the previous year, which found that one year of exercise training did not alter left ventricular function in 16 healthy sedentary men (Sadaniantz, Yurgalevitch, Zmuda & Thompson 1996). Exercise consisted of 4 one-hour supervised training sessions per week with subjects exercising at 60-80% of their measured maximal heart rate. Maximal exercise capacity increased by 27% but there were no significant differences in left ventricular systolic or diastolic function. There was a small decrease in A-wave peak flow velocity after training, but, as the authors point out, although this can indicate improved diastolic function due to enhanced early filling (A-wave velocity is a measure of late filling), it can also be due to a decrease in heart rate as the longer diastolic period will also enhance early filling. It is notable that all these subjects were overweight and the study design ensured that weight was not lost with training, which again demands consideration of the effect of body composition on diastolic function. Although weight was not lost there could have been significant loss of fat mass and gain in muscle mass.

The above is a small but representative selection of studies that have all used healthy subjects of various ages. The effects of exercise training in patients with coronary heart disease and/or left ventricular dysfunction have been less extensively researched.

The safety of exercise training in patients with left ventricular dysfunction following myocardial infarction has been demonstrated by a number of authors. Giannuzzi et al

(1993) investigated the effects of a six-month training programme on left ventricular dimensions and function in 49 patients following anterior myocardial infarction compared to a matched control group. A significant increase in work capacity occurred only in the exercise group. There were no differences in left ventricular dimensions or function between the two groups. Patients with more impaired left ventricular function (ejection fraction \leq 40%) at entry demonstrated further global and regional left ventricular dilation at 6 months, but again there was no difference between the groups. They concluded that post myocardial infarction patients, even those with large anterior infarctions, may benefit from exercise training without any additional negative effects on left ventricular size and topography.

Some of the same authors (Giannuzzi, Temporelli, Corrà & Travazzi, 2003) further investigated the effects of six-months of moderate exercise training on left ventricular remodeling (change in size and shape - usually detrimental to function), work capacity and quality of life in 45 patients with stable heart failure compared to 45 matched controls. In the training group left ventricular dilation decreased ($p < 0.05$) whereas it increased in the control group ($p < 0.01$). Ejection fraction improved in the training group ($p < 0.001$) but was unchanged in the control group. Measures of work capacity and quality of life also improved in the training group but not in the controls. The authors concluded that exercise training is safe and effective in patients with stable heart failure and attenuates abnormal remodeling.

Similar findings on the safety and efficacy of exercise training in myocardial infarction patients were found by Dubach et al (1997). In a small scale study 25 patients with reduced ventricular function following myocardial infarction (mean ejection fraction $32.3 \pm 6\%$) were randomized to a residential 2-month high intensity exercise programme (n=12) or a control group (n=13). They found that the training group achieved a substantial increase in exercise capacity with no deleterious effects on left ventricular dimensions or function. A follow up study of these patients at one year after randomization (Myers et al, 2000) found that the improvements in exercise capacity were sustained and there were still no deleterious effects on left ventricular dimensions or function. Ejection fraction, left ventricular end diastolic and end systolic volumes did not change at any measurement point. During the ten months following the conclusion of the exercise programme it was noted that the exercise group spent a significantly greater time per week undertaking what was classed a vigorous activity than the control group, which may account for the sustained improvement in exercise capacity.

This study confirmed the quality of life benefits of high intensity exercise training previously demonstrated by Adachi et al (1996) in a study of 29 patients with impaired left ventricular function following myocardial infarction. The subjects were divided into a control group, a low intensity training group or a high intensity training group. The intensity was determined individually according to the gas exchange threshold of each patient. Patients then exercised twice daily, 5 days a week for 2 months.

Exercise capacity increased in both training groups, but left ventricular stroke volume and ejection fraction, after 6 minutes of heavy intensity constant work rate, improved significantly only in the high intensity training group. Stroke volume was also significantly increased at rest in the high intensity group. However, stroke volume is not the same as ejection fraction. Stroke volume is the actual volume of blood (in millilitres) ejected from the left ventricle during systole, whereas ejection fraction is the percentage of blood in the ventricle at end diastole that is ejected during systole. In this study all groups significantly reduced their heart rate after training, both at rest and after 6 minutes heavy intensity constant work rate, thereby lengthening diastole and increasing end diastolic volume. Therefore the same ejection fraction will produce a higher stroke volume, and this is exactly what was seen in this study. Therefore, the improvement in left ventricular function is likely to be at least partly due to lower heart rate rather than improved contraction.

The benefits of intensive exercise training in patients with reduced left ventricular function secondary to coronary heart disease were further confirmed in a study by Goebbels et al (1998). Sixty-seven patients one month after myocardial infarction or coronary artery bypass surgery were randomized to either an exercise (n=34) or control group (n=33). The exercise group underwent an 8-week residential programme of twice daily exercise training. Patients in each group were subdivided for analysis according to their ejection fraction. In the exercise group, patients with reduced ejection fraction increased their peak oxygen consumption (a measure of exercise capacity) significantly, whereas those with a normal ejection fraction did not.

In the control group the converse was seen. Patients with a normal ejection fraction improved spontaneously, whereas those with a reduced ejection fraction did not. The authors concluded that patients with reduced left ventricular function benefit strongly from exercise training.

The most recent study in this area used echocardiography and treadmill testing to examine the effects of an exercise based cardiac rehabilitation programme on left ventricular diastolic function and its relation to exercise capacity in patients with coronary heart disease (Yu et al, 2004). This was on a larger scale than previous studies (n=269) with a reasonable follow-up period of 8 months. Patients were randomized to either a control group or an exercise group who undertook an 8-week training programme (2 hours, twice weekly), followed by a 6-month daily walking programme for 1 hour.

Significant improvements in echocardiographic markers of diastolic dysfunction were seen in the exercise group, particularly a sub-group with abnormal relaxation pattern, which correlated with improved exercise capacity. Exercise had a neutral effect on markers of systolic function (ejection fraction and left ventricular diameters). In the control group the prevalence of diastolic dysfunction was increased at the 8-month follow up. The authors concluded that the exercise programme prevented the progression of left ventricular diastolic dysfunction and the improvement in diastolic function predicted the gain in exercise capacity. However, no data was given on the effects of the exercise on body composition. Therefore it is impossible to determine if

the improvement in diastolic function is entirely due to the effect of exercise or whether beneficial changes in body composition could have played a part. Data was given on pre and post training heart rates in both groups, which did not significantly differ. Therefore a slower post training heart rate was not responsible for the improvement in diastolic function seen in the exercise group.

Finally it must be remembered that exercise training does not just affect the left ventricle and that left ventricular output is not solely dependent on left ventricular function. Several authors have demonstrated that patients with coronary artery disease have impaired endothelial function and reduced flow-mediated vasodilatation. This leads to increased peripheral vascular resistance (a crude measure of afterload) which impedes left ventricular outflow. Walsh et al (2003) demonstrated that patients with coronary artery disease had impaired flow-mediated vasodilatation compared to a group of healthy controls. They further demonstrated that these patients had improved flow mediated dilation following an eight week training period (from $3 \pm 0.8\%$ to $5.7 \pm 1.1\%$, $p < 0.05$). Furthermore, although the exercise was predominantly lower limb training the increase in flow-mediated vasodilatation was demonstrated in the brachial artery (arm), indicating that the training effect was generalized and not restricted to the vessels of the exercising muscle bed.

Their results confirmed those of an earlier study by Hambrecht et al (1998), who demonstrated that cycle ergometry training improved endothelial function and vasodilatation in a group of patients with stable chronic heart failure. Further follow

up of these patients by some of the original authors (Hambrecht et al, 2000a) demonstrated a fall in total peripheral resistance in the exercise group compared to a small increase in the control group ($p=0.003$). A fall in peripheral vascular resistance will tend to aid left ventricular outflow and in this study there was indeed a significant increase in mean left ventricular stroke volume in the exercise group (14ml, SD ± 22 in the exercise group vs 1ml, SD ± 19 in the control group, $p=0.03$).

Another study by Hambrecht et al (2000b) demonstrated that exercise had a similar effect on coronary vessels in patients with coronary artery disease. After four weeks of cycle ergometry training, the exercise group ($n=10$) had a 29% increase in coronary artery flow reserve compared to a control group ($n=9$), ($p<0.01$). Logically this improvement in coronary blood flow should have the potential to improve left ventricular systolic and diastolic (since this also requires energy) function. This is an important finding since it may allow greater understanding of how exercise can benefit ventricular function.

This finding therefore demands consideration of the well described phenomena of myocardial stunning and hibernation, both important causes of myocardial dysfunction in patients with ischaemic heart disease (Rinaldi & Hall, 2000).

Myocardial stunning refers to the transient dysfunction of myocardium secondary to an acute ischaemic insult, such as post myocardial infarction or post coronary artery bypass grafting. Obviously infarcted myocardium cannot recover but areas of myocardium adjacent to the area of infarction are often subject to stunning, and,

following restoration of normal blood flow, recover normal function after a few days. Also, in these days of rapid thrombolysis or angioplasty for patients presenting with acute myocardial infarction, considerable areas of myocardium will be 'rescued' from infarction but remained stunned for anything from a few hours to a few days afterwards, depending largely on the severity and duration of the ischaemic event.

The significance of this in relation to this study is in the timing of the initial echocardiogram. If the initial echocardiogram is performed too early after acute myocardial infarction or troponin positive acute coronary syndrome, there may be a considerable degree of left ventricular dysfunction observed due to myocardial stunning, which would resolve spontaneously within days. It is therefore important that the initial echocardiogram is not done too soon so that any significant improvement in left ventricular function seen in the repeat echocardiogram is not simply the result of spontaneous resolution of myocardial stunning.

Hibernation refers to areas of myocardium which have become dysfunctional probably due to chronic myocardial ischaemia. This myocardium is viable but does not contribute to the myocardial workload due to the lack of an adequate blood supply. Initially this 'downregulation' of function is thought to be a protective mechanism. By reducing metabolic demand the myocardium is protected from the ongoing ischaemia (Rinaldi & Hall, 2000). However, if this persists for some time, cellular degeneration and fibrosis can occur (Mari & Strauss, 2002).

The findings of Hambrecht et al (2000b), that exercise increases coronary artery flow reserve, begs the question 'to what extent does any of that increased flow reach areas of hibernating myocardium'?

Heyder, Engel & Hörmann (1996) demonstrated that angioplasty of chronically occluded coronary arteries had a beneficial effect on left ventricular function. Out of 34 patients, 25 (73.5%) showed improvement of regional ventricular function, with mean ejection fraction increasing from 56.9% to 64.1% ($p < 0.001$). They concluded that this improvement was due the presence of hibernating myocardium which regained functionality following angioplasty.

That exercise can also improve perfusion of hibernating myocardium was demonstrated by Belardinelli, Georgiou & Purcaro (1998). A group of 71 patients with ischaemic myocardial dysfunction were divided in to a training group and a non-exercising control group. The training group underwent 10 weeks of moderate exercise training.

The presence of hibernating myocardium in some of these subjects was demonstrated by dobutamine stress echocardiography. Following training, only the trained group showed a significant improvement in ejection fraction in response to peak dobutamine levels. The authors found that the presence of hibernating myocardium at baseline predicted the magnitude of improvement. Adding to the theory that this was due to improved perfusion of hibernating myocardium was the fact that 73% of

exercise tolerance tests that were positive for inducible ischaemia at baseline became negative following training ($p < 0.001$ vs controls). It is not clear from this study whether the improved perfusion of hibernating myocardium was due to improved flow mediated vasodilatation of diseased coronary vessels or the development of collateral vessels.

The long held belief that hibernating myocardium is due to reduced resting blood flow is currently being questioned. A recent review by Camici & Rimoldi (2003) into the use of positron emission tomography to identify hibernating myocardium claimed that resting blood flow to hibernating myocardium is not different from that in healthy volunteers in the majority of cases. They claim the main feature of hibernating myocardium is severely reduced coronary vasodilator reserve that improves after revascularization in parallel with ventricular function. The cardiac rehabilitation community needs to know if exercise would have a similar effect.

Another study using positron emission tomography (Voipio-Pulkki, 1998) suggested that exercise in heart failure patients may normalize resting myocardial hypoperfusion, possibly through the recruitment of coronary collaterals. It therefore remains unclear to what extent resting myocardial blood flow is impaired in hibernating myocardium, whether exercise (and pharmacological measures), rather than revascularization, has the potential to increase perfusion of hibernating myocardium and if so is this by improved coronary artery flow reserve or recruitment of collaterals.

Certainly positron emission tomography has the potential to add a great deal of information as to the mechanisms by which exercise improves myocardial perfusion and ventricular performance, especially if used in combination with dobutamine stress echo (Barrington et al, 2004), thereby allowing the simultaneous measurement of both function and perfusion. This would allow visual confirmation that areas of myocardium with improved perfusion also exhibited improved performance.

Unfortunately positron emission tomography, although often seen as the 'gold standard' for differentiating potentially functional myocardium from fibrotic tissue, is not available in all centres. Magnetic resonance imaging with gadolinium enhancement (currently an off-license application) is also able to differentiate hibernating from non-viable myocardium with high sensitivity and specificity (Grand & Bluemke, 2006) but access to this service is also limited. However, similar results/information can be obtained with myocardial perfusion imaging techniques using thallium or technetium⁹⁹ radio-isotopes, which are more readily accessible (Mari & Strauss, 2002).

In summary, exercise may improve left ventricular function systolic and/or diastolic function. This may be achieved directly, possibly by increasing coronary blood supply through increased coronary vasodilator reserve or collateral development, and/or by reducing peripheral vascular resistance.

This is a brief review of some of the more recent literature available on the effects of exercise training on left ventricular function in a variety of patient groups and normal subjects of various ages and with a variety of exercise histories. Studies conducted prior to the advent of thrombolysis for acute myocardial infarction (the latter half of the 1980's) have not been included as patients in those studies may have had larger areas of infarcted myocardium and less hibernating myocardium. It is important that studies reviewed in relation to the present study are relevant to contemporary patients. The studies reviewed above serve to illustrate a diversity of research methods and results, many of which are conflicting.

Resources available to most cardiac rehabilitation services in the UK do not allow long term supervised exercise programmes, as used in some of these studies. However, the latest study (Yu et al, 2004) produced encouraging results over a supervised exercise period similar to that which most cardiac rehabilitation programmes provide. Many cardiac rehabilitation programmes (including that run by this author) are now also arranging for long term exercise opportunities (Phase 4) following the supervised programme (as in the study by Yu et al, 2004).

The number of patients with a diagnosis of heart failure referred to cardiac rehabilitation programmes is likely to increase as beneficial effects of exercise on quality of life are obvious. Also, as demonstrated by Velazquez et al (2004), 42% of patients with myocardial infarction, a patient group commonly referred to cardiac rehabilitation, have some degree of heart failure or left ventricular dysfunction. This

means it is important for cardiac rehabilitation providers to study the effects of their exercise programmes on left ventricular function in order to determine the optimum exercise strategy for these patients and in so doing provide a scientific basis for the development of specific heart failure rehabilitation programmes.

This study sought to examine the effects of the cardiac rehabilitation programme coordinated by the author on left ventricular function in patients with recent myocardial damage (myocardial infarction or troponin positive acute coronary syndrome) and any degree of left ventricular systolic dysfunction. As demonstrated in the studies above, this programme has the potential to have a positive effect on left ventricular systolic function, diastolic function, both or neither. It is important to note that no study has shown exercise to have a detrimental effect on any aspect of left ventricular function.

Methods

Subjects

Patients admitted to the coronary care unit or medical assessment unit at Noble's Hospital with acute myocardial infarction (ST elevation on electrocardiograph (ECG)) or troponin positive acute coronary syndrome (troponin I >0.04) were potential subjects. Those patients who had any degree of impaired left ventricular systolic function, demonstrated on initial echocardiogram, defined as an ejection fraction of $<55\%$, were invited to take part in the study. Of the people who agreed, those who completed the cardiac rehabilitation programme formed the study (exercise) group and those who declined formed the control group.

It is recognised that as people get older their ability to exercise declines, often secondary to the development of various musculo-skeletal problems such as arthritis. Local unpublished data has also indicated that some elderly people have difficulty traveling to the hospital based cardiac rehabilitation programme, or simply do not believe that gym based exercise is suitable for them. As illustrated in the above review of the existing research, aging also has a detrimental effect on left ventricular function (except in endurance athletes). Therefore, in order to avoid the control group being significantly older than the study group, and consequently with poorer left ventricular function at baseline, there was an upper age limit of 75 years.

Since the aim of this study was to assess the effects of exercise in patients with left ventricular dysfunction from an ischaemic cause, patients with pre-existing left ventricular dysfunction from other causes were excluded. These included dilated cardiomyopathy and hypertrophic obstructive cardiomyopathy.

Patients who had other conditions that affected the echocardiographic measurement of left ventricular function were also excluded from the study. These included previous mitral and aortic valve surgery, pacemaker implant and left ventricular aneurysm. Also in this category were patients who were transferred early in their recovery period to the regional Cardiothoracic Centre for a revascularization procedure (percutaneous trans-coronary angioplasty or coronary artery bypass grafting). Revascularization would form a confounding factor since this in itself could affect left ventricular function (Heyder, Engel & Hörmann, 1996).

Patients who were unable to undertake gym based exercise for cardiac reasons (e.g. aortic stenosis, hypertrophic obstructive cardiomyopathy) were also excluded from the study. Patients who were unable to undertake gym based exercise for other reasons (e.g. arthritis, unable to travel to the hospital gym) were eligible to be included in the control group.

Ethical approval was sought from, and granted by, the Local Research Ethics Committee and by the Research Ethics Committee of the Centre for Exercise & Nutrition Science, University of Chester.

Potential subjects were given a verbal description of the study by the author, followed by a written description for their perusal (Appendix 1). If they agreed to take part they were asked to sign a consent form (Appendix 2).

Design

The study used a repeated measures design. The dependent variables were the heart rate and the various echocardiographic measures that allowed an assessment of left ventricular function (systolic and diastolic). These were ejection fraction (Simpson's method), isovolumetric relaxation time, trans-mitral E and A wave size and ratio and E wave deceleration time. Any valvular regurgitation was also noted.

The independent variable was whether the subject completed the exercise based cardiac rehabilitation programme or had usual care without cardiac rehabilitation.

Various drugs used in cardiology have effects on left ventricular function, such as beta-blockers, ACE inhibitors and nitrates. It was impossible to control for the use of these drugs due to obvious ethical considerations, but the drug therapy of each subject at the time of the echocardiograms was noted so that any differences in drug therapy between the two measurements could be taken into account.

Apparatus

Echocardiograms were performed using a GE/Vingmed Vivid 7 echocardiography machine. The data collection form is shown in Appendix 3.

The exercise equipment used in the cardiac rehabilitation gym was arranged in two circuits of thirteen exercises consisting of the following:

Table 1. Exercise circuits.

Circuit 1	Circuit 2
Cross trainer (Pulse Fitness)	Cross Trainer (Hogarth Health)
Free weights (dumbbells for arm exercises)	Free weights (dumbbells for arm exercises)
Treadmill (Pulse Fitness)	Treadmill (Pulse Fitness)
Static exercise cycle (Pulse Fitness)	Static exercise cycle (Pulse Fitness)
Press-ups against wall-bars	Press-ups against wall-bars
Stepper (Pulse Fitness)	Stepper (Pulse Fitness)
Static exercise cycle (Pulse Fitness)	Leg-press (Pulse Fitness)
Concept II rowing machine	Concept II rowing machine
Light punch-bag	Light punch-bag
Step-ups on 9" step	Step-ups on 9" step
Balance on wobble-board	Balance on wobble-board
Free weights (dumbbells for arm exercises)	Free weights (dumbbells for arm exercises)
Jogging on trampet	Jogging on trampet

Procedures

The echocardiographer (at Noble's hospital it tends to be the same person except when he is on leave) was asked to make some specific measurements in patients who were potential subjects. The measurements were those that allowed an assessment of left ventricular function (systolic and diastolic). These were ejection fraction (Simpson's method), isovolumetric relaxation time, trans-mitral E and A wave size and ratio and E wave deceleration time. Any valvular regurgitation was also noted.

The ejection fraction is a measure of the systolic function and the other measurements are indicative of diastolic function. Simpson's method was chosen for estimation of ejection fraction for reasons explained in the introduction. Further explanation of these measurements is given in the discussion section.

Where possible the initial echocardiogram was performed at least 3 days post initial event to minimize the effects of early myocardial stunning, but the range was 2-6 days depending on the workload of the echocardiographer and in some cases the medical urgency of the echocardiogram.

Subjects completing the cardiac rehabilitation programme had a repeat echocardiogram within 1 week of completing the course. For most subjects this was approximately 3 months after the index event. Subjects forming the control group had a repeat echocardiogram after a similar time period from their index event. Wherever possible all echocardiograms were performed by the same operator in order to

eliminate, as far as possible, any inter-observer variations in measurements. The echocardiographer was not informed by the researcher as to which patients were in the exercise group and which were controls, although general conversation during the examination could have revealed this.

Subjects in the exercise group completed a standardized 6 week cardiac rehabilitation programme, beginning approximately 6 weeks after their index event, and consisting of two 50 minute exercise sessions per week using the equipment described above (Table 1). This took the form of timed circuit training under the direction of the cardiac rehabilitation physiotherapist. The first session of each patient's course comprised instruction, demonstration and practice in the use of the equipment. The remaining eleven sessions were normal exercise sessions. They were also encouraged to undertake other exercise, such as daily brisk walking, although to what extent the patients undertook this activity was not recorded. The rehabilitation programme also included education and stress management, which is the usual format for cardiac rehabilitation programmes in the British Isles.

Subjects in the control group received usual care without the cardiac rehabilitation programme. Usual care included advice from the cardiac rehabilitation nurses to try to maximize their exercise potential through daily activities such as walking.

All subjects were assured of anonymity in any published report. They could be identified by means of their hospital number on the data analysis file and by their other details on the data collection form (appendix 3), but only the researcher and his supervisors had access to this information.

Patients were assured that they were free to withdraw from the trial at any time. Those requesting feedback following the repeat echocardiogram were told of any changes in their left ventricular function and the significance (if any) of this information was explained to them by the researcher.

Statistical Analysis

The type of data collected, i.e. the echocardiographic measurements, heart rate and age, is ratio and therefore could be subjected to parametric testing methods (paired t-tests). However, the sample size is small and some of the data is skewed. Therefore non-parametric testing is indicated. The within group comparison data was analysed by use of the Wilcoxon Signed Ranks Test, and independent group comparison data was analysed by use of the Mann-Whitney U Test. As in most medical research the level of significance was taken as $p \leq 0.05$.

Data was analysed using SPSS version 12.0.

Results

Subject Groups

As previously described the groups were self-selecting according to their willingness or ability to undertake the cardiac rehabilitation course. No degree of control over eligible subjects was exercised. To date twelve male subjects (median age 59 years, interquartile range 56 – 67.75) and five female subjects (median age 70 years, interquartile range 55 - 72) have been recruited to the study. Eight patients are in the exercise group (one female) and nine patients are in the control group (four female). Eventually twenty patients will be required in each group for statistical significance and recruitment continues at the time of this interim report.

Measurements

The following tables show the age, heart rate, weight and echocardiographic measurements taken in both groups at baseline and repeat (post) measuring. Independent group comparison statistics are given at baseline and within group comparisons at repeat testing.

The meanings of the measurements are given in the discussion section (below).

Table 2. Baseline Measurements and Independent Group Comparison Statistics

Variable	Exercise group* (n=8)	Control group* (n=9)	Independent group comparison statistic
Age	58.0 (50 – 67.5)	70.0 (58.0 – 72.0)	P= 0.111
Ejection fraction (%)	43.0 (34.1 – 48.4)	49.5 (33.7 – 51.9)	P= 0.386
Isovolumetric relaxation time (ms)	99.8 (72.1 – 124.8)	105.4 (94.3 – 114.6)	P= 0.699
E-wave size (m/s)	0.93 (0.64 – 1.15)	0.60 (0.53 – 1.23)	P= 0.500
E-wave duration (ms)	407.6 (304.5 – 532.4)	327.2 (304.1 – 403.0)	P= 0.290
E-wave deceleration time (ms)	335.9 (259.8 – 437.6)	475.5 (386.8 – 609.7)	P= 0.043
A-wave size (m/s)	0.68 (0.62 – 0.88)	0.95 (0.73 – 1.12)	P= 0.043
A-wave duration (ms)	135.9 (115.1 – 153.9)	127.5 (116.5 – 143.3)	P= 0.469
E-A ratio	1.28 (0.96 – 1.39)	0.81 (0.51 – 1.28)	P= 0.068
Heart rate (resting)	59.5 (53.8 – 63.8)	65.0 (61 – 70.5)	P= 0.193
Weight (Kg)	76.5 (68.7 – 93.7)	85.5 (65.1 – 102.3)	P= 0.700

*All values median (interquartile range)

Table 2 shows the independent group comparison statistics between the exercise and control groups at baseline. There are no statistically significant differences between the two groups for age, heart rate, weight or ejection fraction (systolic function). Two of the measures of diastolic function, E-wave deceleration time and A-wave size, do appear to be statistically different ($p=0.043$ in both cases). This may be due to the very small sample size and may disappear when recruitment is complete. However, some of the individual E-wave deceleration times in both groups are unusually long (normal range 200 ± 33), which is reflected in the interquartile range. This is likely to be due to the difficulties in determining the exact onset and termination of the E-wave slope, which is a well recognized problem in echocardiography, as the pictures are often unclear and demand a considerable degree of professional judgment. Consequently, this data has not been analysed further at this stage.

Table 3. Exercise Group Baseline and Repeat Measurements

Variable	Baseline*	Repeat*	Within group comparison statistic†
Ejection fraction (%)	43.0 (34.1 – 48.4)	58.6 (49.6 – 64.1)	P=0.025
Isovolumetric relaxation time(ms)	99.8 (72.1 – 124.8)	80.4 (67.9 – 99.8)	P=0.207
E-wave size (m/s)	0.93 (0.64 – 1.15)	0.93 (0.69 – 1.16)	P=0.484
E-wave duration (ms)	407.6 (304.5 – 532.4)	354.9 (307.8 – 422.8)	P=0.398
A-wave size (m/s)	0.68 (0.62 – 0.88)	0.76 (0.62 – 0.97)	P=0.345
A-wave duration (ms)	135.9 (115.1 – 153.9)	138.7 (124.8 – 153.5)	P=0.779
E-A ratio	1.28 (0.96 – 1.39)	1.12 (1.05 – 1.26)	P=0.779
Heart rate (resting)	59.5 (53.8 – 63.8)	64.0 (60.5 – 68.5)	P=0.575
Weight (Kg)	76.5 (68.7 – 93.7)	77.1 (67.1 – 94.3)	P= 0.865
Left ventricular end-diastolic volume (mls)	136.8 (134.5 – 157.1)	144.1 131.7 – 158.0)	P=0.779

*All values median (interquartile range)

† Wilcoxon Signed Rank Test

Table 3 shows the Wilcoxon Signed Rank Test statistics for pre and post measurements in the exercise group. This shows a statistically significant increase in ejection fraction following the exercise course (median EF pre 43.0%, median EF

post 58.6%, $p=0.025$). This equates to a 36.3% relative improvement. If statistical significance is maintained when recruitment is completed the null hypothesis for this measurement can be rejected. There are no statistically significant differences in heart rate, weight or any measure of diastolic function.

Table 4. Control Group Baseline and Repeat Measurements

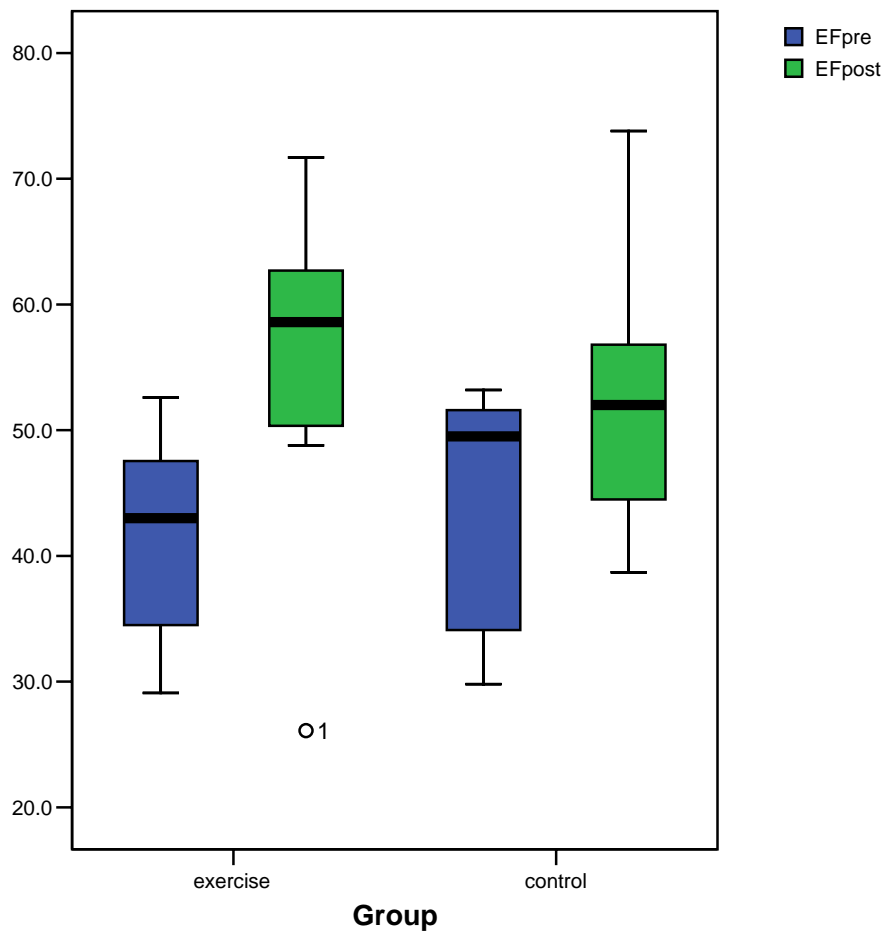
Variable	Baseline*	Repeat*	Within group comparison statistic †
Ejection fraction (%)	49.5 (33.7 – 51.9)	52.0 (43.6 – 58.4)	P=0.139
Isovolumetric relaxation time (ms)	105.4 (94.3 – 114.6)	110.9 (97.1 – 133.1)	P=0.286
E-wave size (m/s)	0.60 (0.53 – 1.23)	0.77 (0.61 – 0.98)	P=0.767
E-wave duration (ms)	327.2 (304.1 – 403.0)	332.7 (231.1 – 478.8)	P=0.767
A-wave size (m/s)	0.95 (0.73 – 1.12)	0.86 (0.72 – 1.02)	P=0.374
A-wave duration (ms)	127.5 (116.5 – 143.3)	149.7 (133.1 – 172.8)	P=0.012
E-A ratio	0.81 (0.51 – 1.28)	0.72 (0.61 – 1.29)	P=0.953
Heart rate (resting)	65.0 (61 – 70.5)	64.0 (58.0 – 72.5)	P=0.889
Left ventricular end-diastolic volume (mls)	119.1 (103.1 – 142)	123.4 (89.4 – 142.0)	P=0.374

*All values median (interquartile range)

† Wilcoxon Signed Rank Test

Table 4 shows the Wilcoxon Signed Rank Test statistics for pre and post measurements in the control group. In contrast to the exercise group there is no statistically significant difference in ejection fraction between measurements in the control group (median EF pre 49.5%, median EF post 52%, $p=0.139$). There does appear to be a statistically significant difference in A wave duration (median A wave duration pre 127.5 milliseconds, median A wave duration post 149.7 milliseconds, $p=0.012$). There are no statistically significant differences in any of the other measurements of diastolic function or in heart rate. The control group subjects were not re-weighed.

Figure 1. Boxplot summarizing the median, quartiles and extreme values of ejection fraction (%) pre & post measurements



This boxplot shows an increase in ejection fraction in both groups at the time of the second (post) measurement. However the increase in ejection fraction in the exercise group is greater than that in the control group. The increase in the exercise group is statistically significant ($p=0.025$), whereas it is not in the control group ($p=0.139$). Note there is one extreme outlying value in the exercise group.

Discussion

This study sought to determine whether or not the exercise-based cardiac rehabilitation programme coordinated by the author had a beneficial effect on left ventricular systolic and/or diastolic function in patients with recent myocardial damage (myocardial infarction or troponin positive acute coronary syndrome) and any degree of left ventricular systolic dysfunction (defined as a left ventricular ejection fraction of <55%). Previous similar studies have produced conflicting results for both parameters.

In this study, at the time of this interim report, there is a statistically significant improvement in mean left ventricular ejection fraction, i.e. systolic function, in the exercise group (median EF pre 43.0%, median EF post 58.6%, $p=0.025$). The control group also shows a small improvement in ejection fraction but this is not statistically significant (median EF pre 49.5%, median EF post 52%, $p=0.139$).

The only other statistically significant difference at this stage is a lengthening of A-wave duration in the control group (median A wave duration pre 127.5 milliseconds, median A wave duration post 149.7 milliseconds, $p=0.012$). In the absence of significant differences in any other measure of diastolic function this is difficult to explain and may be due to small sample size or measurement error.

Echocardiography requires a considerable degree of judgment and the clarity of images obtained do not always permit precise measurements, as explained in the results section.

Consideration of Valvular Function

The ejection fraction is the percentage of blood in the left ventricle at the end of diastole that is ejected when the ventricle contracts. The normal range is 55-85%. The majority of the blood should be ejected in a forward direction through the aortic valve and into the aorta. In many patients in the age group involved in this study there is some degree of mitral regurgitation, where blood is forced back through the mitral valve during left ventricular contraction (systole). If this mitral regurgitation is severe the ejection fraction does not adequately describe systolic function, since the more blood that goes back through the mitral valve the lower the true cardiac output will be for any given ejection fraction.

Also, over-distension of the left atrium in this scenario will effect diastolic filling of the left ventricle and significantly affect measures of diastolic function. Since the measurement of ejection fraction is done purely by measuring the change in volume of the left ventricle between the end of diastole and the end of systole, this does not take into account the direction of outflow. Also aortic valve stenosis can significantly impede left ventricular outflow. Therefore echocardiographic measures of left ventricular function can be significantly affected by dysfunction of mitral and/or aortic valves, hence the importance of noting any valvular dysfunction on the echocardiograms.

In this study to date, most patients have had either normal mitral function or mild regurgitation. One patient in the exercise group had moderate mitral regurgitation at both pre and post testing. This patient showed some aspects of a restrictive filling pattern at baseline which worsened slightly at repeat testing (E-wave size $>1.2\text{m/s}$, E:A ratio >2 ; see table 5 below). Two patients in the control group had mild mitral regurgitation at baseline which became moderate on repeat testing. One of these patients developed some aspects of slow relaxation pattern on repeat testing (IVRT $>110\text{ms}$, E-wave size $<0.5\text{m/s}$, E:A ratio <1.0 ; see table 5 below). None have exhibited severe mitral regurgitation. Two patients on the exercise group and three on the control group have shown mild aortic regurgitation but no patients have demonstrated any degree of aortic stenosis. These findings are unlikely to have any significant effect on the measurements of left ventricular function in this study.

Effects on Left Ventricular Systolic Function

The positive effect of exercise on left ventricular ejection fraction seen in this study is supported by the studies by Giannuzzi, Temporelli, Corrà & Travazzi (2003) and by Adachi et al (1996).

Giannuzzi, Temporelli, Corrà & Travazzi (2003) used six months of moderate exercise training in 45 patients with stable chronic heart failure (ejection fraction $\leq 35\%$, mean $25 \pm 4\%$) and usual care with no supervised exercise in 45 matched

controls. Exercise consisted of 30 minutes cycle ergometry 3-5 times a week at 60% peak VO_2 and they were asked to do a daily brisk walk of 30 minutes (compliance reported as 85%). Ejection fraction increased by 16% in the exercise group ($p=0.01$) with no improvement in the controls.

In the study by Adachi et al (1996) the improvement seen at rest was in stroke volume rather than in ejection fraction and this was likely to be mostly due to a lower post training heart rate lengthening diastole and increasing end diastolic volume. Therefore the same ejection fraction will produce a higher stroke volume, and this is exactly what was seen in this study. However, it is notable that the lower intensity exercise group reduced their heart rates more than the high intensity group (76 ± 13 to 65 ± 9 , $p=0.002$, in the low intensity group vs 76 ± 10 to 70 ± 10 , $p=0.006$, in the high intensity group). Both groups increased stroke volume at rest but only the high intensity group achieved significance level. This suggests that the lower heart rate only partially accounted for the increased stroke volume and there may have been an increase in systolic work in the high intensity group. It was only in the high intensity group that ejection fraction increased significantly after six minutes of heavy intensity constant work rate, suggesting that high intensity training does increase systolic function.

Results to date in the present study show a 32.9% relative improvement in ejection fraction in the exercise group ($p=0.025$). Giannuzzi, Temporelli, Corrà & Travazzi (2003) used a training intensity similar to that used in the present study but their

training was more frequent (3-5 times per week plus daily brisk walking, compared to twice a week and daily brisk walking) and lasted longer (six months compared to six weeks). Despite this more frequent and prolonged training schedule their study produced a smaller improvement in ejection fraction than in the present study.

There are a number of possible reasons for this (other than the small numbers so far recruited). Firstly, this assumes that the improvement seen in the present study to date is maintained at the end of recruitment, of course that may not prove to be the case. Secondly, Giannuzzi, Temporelli, Corrà & Travazzi (2003) included patients with stable chronic heart failure from causes other than ischaemic heart disease (67% ischaemic heart disease, 27% dilated cardiomyopathy and 6% valvular disease). It is possible that patients with dilated cardiomyopathy and valvular disease did not improve their ejection fraction as much as the patients with ischaemic heart disease; however this sub-group analysis is not reported. In any case, sub-group analysis is inherently unreliable since the characteristics or factors matching the original study and control groups may not be maintained in the sub-groups.

Thirdly, beta-blockers, a group of drugs commonly used in patients with ischaemic heart disease and heart failure, slow heart rate, improve left ventricular function and attenuate ventricular remodeling. In the study by Giannuzzi, Temporelli, Corrà & Travazzi (2003) only 22% of patients in their exercise group were taking beta-blockers, whereas 87.5% of patients in the present study's exercise group were doing so. This is likely to have had some influence on the results, although it is impossible

to quantify this.

In contrast to the study by Adachi et al (1996), in the present study heart rate did not reduce significantly (or indeed at all) post training in the exercise group (median 59.5 pre-training; 64.0 post training, $p=0.575$). This is likely due to the fact that all but one of the patients (87.5%) were taking beta-blockers at the time of both pre and post training measurements. In the study by Adachi et al (1996), beta-blockers were withheld throughout the study period (something unlikely to receive ethical approval today) so the reduction in heart rates seen is likely to be a training effect. The authors speculate that the reduction in heart rate seen in the control group could be due to the fact that activities of daily living of some patients in this group could be similar to the prescribed physical training in the low intensity training group. As explained above, slowing of the heart rate will tend to increase end diastolic volume and therefore improve stroke volume by means of the Frank Starling mechanism (which basically states that, up to a point, the more a muscle fibre is stretched the greater the force of elastic recoil when the muscle contracts).

Thus in the study by Adachi et al (1996) improvements in left ventricular systolic function are likely due to a combination of lower post-training heart rate and increased systolic work, whereas in the present study improvements can only be due to improved systolic work, as there was no change in heart rate or measures of diastolic function. In particular there was no significant increase in left ventricular end-diastolic volume (median volume pre 136.8mls, interquartile range 134.5 –

157.1; median volume post 144.1, interquartile range 131.7 – 158.0, $p=0.799$), which correlates with the lack of a decrease in heart rate. This suggests that the increase in ejection fraction is due to increased systolic work rather than increased end-diastolic stretch (Frank Starling mechanism).

At present it is only possible to speculate on the possible mechanisms responsible for this improvement in the light of previously published research. The most likely mechanisms seem to be either reduced peripheral vascular resistance (i.e. reduced afterload) and/or the recruitment of hibernating myocardium secondary to improved coronary blood flow.

Patients with coronary artery disease are known to have impaired endothelial function and reduced flow-mediated vasodilatation. This leads to increased peripheral vascular resistance (a crude measure of afterload) which impedes left ventricular outflow.

Walsh et al (2003) demonstrated that patients with coronary artery disease had impaired flow-mediated vasodilatation compared to a group of healthy controls. They further demonstrated that these patients had improved flow mediated dilation following an eight week training period (from $3 \pm 0.8\%$ to $5.7 \pm 1.1\%$, $p < 0.05$).

Furthermore, although the exercise was predominantly lower limb training the increase in flow-mediated vasodilatation was demonstrated in the brachial artery (arm), indicating that the training effect was generalized and not restricted to the vessels of the exercising muscle bed.

Hambrecht et al (2000a) also demonstrated a fall in total peripheral resistance in the exercise group compared to a small increase in the control group ($p=0.003$) in a study of the effects of exercise ergometry in stable heart failure patients. There was also a significant increase in mean left ventricular stroke volume in the exercise group (14ml, SD ± 22 in the exercise group vs 1ml, SD ± 19 in the control group, $p=0.03$), and in ejection fraction (from 30, $\pm 8\%$ to 35, $\pm 9\%$, $p=0.003$). The changes from baseline in total peripheral resistance in both groups correlated with changes in stroke volume, suggesting that the reduction in afterload had improved left ventricular systolic function.

Hence reduction in peripheral vascular resistance could explain the improvement in ejection fraction seen in the present study and many authors have claimed that this is the likely mechanism by which exercise rehabilitation has this effect.

However, Hambrecht et al (2000b) demonstrated that exercise also has a vasodilatory effect on coronary vessels in patients with coronary artery disease. After four weeks of cycle ergometry training, the exercise group ($n=10$) had a 29% increase in coronary artery flow reserve compared to a control group ($n=9$), ($p<0.01$).

It is known that revascularization techniques improve coronary perfusion and improve left ventricular function, possibly through recruitment of hibernating myocardium. Heyder, Engel & Hörmann (1996) demonstrated that angioplasty of chronically occluded coronary arteries had a beneficial effect on left ventricular

function. Out of 34 patients, 25 (73.5%) showed improvement of regional ventricular function, with mean ejection fraction increasing from 56.9% to 64.1% ($p < 0.001$). They concluded that this improvement was due the presence of hibernating myocardium which regained functionality following angioplasty.

Belardinelli, Georgiou & Purcaro (1998) demonstrated that exercise can also improve perfusion of hibernating myocardium. In a group of 71 patients with ischaemic myocardial dysfunction, hibernating myocardium was demonstrated in some of these subjects using dobutamine stress echocardiography. After 10 weeks training only the exercise group had improved ejection fraction and the presence of hibernating myocardium predicted the magnitude of improvement. Furthermore, 73% of exercise tolerance tests that were positive for inducible ischaemia at baseline became negative following training ($p < 0.001$ vs controls). This strongly suggests that improved perfusion of hibernating myocardium was a significant factor in improving ejection fraction.

Camici & Rimoldi (2003) claim the main feature of hibernating myocardium is severely reduced coronary vasodilator reserve that improves after revascularization in parallel with ventricular function. The study by Belardinelli, Georgiou & Purcaro (1998) suggests that exercise may have a similar effect. If this can be proven this has important implications for the treatment of patients with ischaemic left ventricular dysfunction and hibernating myocardium, especially those for which surgical revascularization may have significant risks, as patients with hibernating myocardium

have a poor prognosis without revascularization (Rinaldi & Hall, 2000).

It also has significant implications for those responsible for NHS budgets, as exercise based cardiac rehabilitation is considerably cheaper than surgical revascularization and targeting funding towards cardiac rehabilitation could potentially allow the treatment of a greater number of patients in a cost effective and safe manner.

If the present study continues to show significant improvements in ejection fraction at the end of recruitment it would be important to investigate whether this is due to recruitment of hibernating myocardium, rather than solely due to reduced peripheral vascular resistance. This could be done by simultaneous assessment of both ventricular function using dobutamine stress echocardiography and ventricular perfusion using positron emission tomography or myocardial perfusion imaging, to determine if improvement in ventricular systolic function correlates with improved perfusion of hibernating myocardium.

Effects on Left Ventricular Diastolic Function

Diastolic function is much more complex to assess than systolic function. Diastolic function relates to the ability of the ventricle to relax (and therefore fill) following systole, in other words the degree of chamber stiffness. This is an active rather than passive action and requires energy. As such it can be affected by myocardial ischaemia, but other conditions can also have an effect. These are left ventricular

hypertrophy (from any cause), cardiomyopathies (especially restrictive), ventricular infiltrations (amyloid, sarcoid, etc.) and pericardial constriction. Also, as discussed earlier, aging tends to reduce diastolic function but this is attenuated if predisposing factors (hypertension, diabetes, obesity, etc.) are not present (Fischer et al, 2003). Some authors have also noted that long-term exercise also attenuates age related declines in diastolic function (Arbab-Zadeh et al, 2004; Palka, Lange & Nihoyannopoulos, 1999). However, other authors have contradicted these findings (Gates, Tanaka, Graves & Seals, 2003; Baldi et al, 2003).

Diastole begins at the point in the cardiac cycle when outflow from the left ventricle ceases and the aortic valve closes. From this point the left ventricle begins to relax but there is no change in left ventricular volume until the mitral valve opens. This period is known as the isovolumetric relaxation time (IVRT) and the normal range is around 48-65 milliseconds (ms) in younger subjects increasing in adults over 40 years of age to around 58-92ms.

When the mitral valve opens blood should flow rapidly from the left atrium into the left ventricle. This early filling period is represented by the E-wave formed by anterior mitral valve leaflet excursion in M-mode echocardiography and trans-mitral flow velocity can be measured (in metres per second, m/s) by pulsed Doppler in the apical 4-chamber view. This velocity will gradually slow as the ventricle fills and the pressure gradient between the left atrium and left ventricle decreases. When the left atrium contracts, trans-mitral flow velocity increases again, producing the A-wave on

the M-mode echocardiogram and again the velocity can be measured by pulsed Doppler.

Two reduced trans-mitral flow patterns are commonly recognized. The ‘slow relaxation pattern’ is associated with myocardial ischaemia and/or left ventricular hypertrophy. It is characterized by prolonged IVRT, small E-wave, large A-wave and reversed E:A ratio (E:A ratio <1). The ‘restrictive pattern’ is associated with cardiomyopathies, constrictive pericarditis and systolic heart failure (among others). It is characterized by a tall E-wave, small A-wave and short IVRT. Table 5 summarizes these patterns.

Table 5. IVRT, E-wave and A-wave values

Parameter	Normal range	Slow relaxation pattern	Restrictive pattern
IVRT (>40 years) (ms)	58 - 92	> 110	< 58
E-wave (m/s)	0.7 – 1.0	< 0.5	> 1.2
A-wave (m/s)	0.45 – 0.75	> 0.8	< 0.3
E:A ratio	>1.0 - <2.0	< 1.0	> 2.0

The present study recruited subjects with reduced systolic function with or without reduced diastolic function. It did not recruit subjects with reduced diastolic function and preserved systolic function. Some subjects did show some indicators of a slow

relaxation pattern at baseline, which could be due to their known ischaemic heart disease. These indicators are a prolonged IVRT in both groups (exercise group median 99.8ms, interquartile range 72.1 – 124.8; control group median 105.4ms interquartile range 94.3 – 114.6), normal range 58-92 in this age group), large A-wave in the control group (median 0.95 m/s, interquartile range 0.73 – 1.12) and reversed E:A ratio in the control group (0.81, interquartile range 0.51 – 1.28). Only the A-wave size shows a statistically significant difference between the two groups at baseline. However, the wide interquartile ranges are notable, and these often overlap the limits of normal range. Reflecting this, only one patient (in the control group) truly had a slow relaxation pattern, which had improved on repeat testing. Other patients in both groups exhibited abnormal filling pattern for some parameters but not others. Median figures may change when recruitment is complete.

As stated above the only statistically significant within-group difference in diastolic parameters at this stage of this study is a lengthening of A-wave duration in the control group at the time of the second measurement (median 127.5 milliseconds at baseline, 149.7 milliseconds at repeat testing, $p=0.012$). However, this is only one parameter and accurate assessment of diastolic function involves taking into account a range of parameters. This change is difficult to explain, especially in the absence of any significant changes in any other diastolic parameter, and at this stage it is possible that it is simply due to the small number of subjects or measurement error. The overall picture is one of no change in diastolic function in either group.

Levy, Cerqueira, Abrass, Schwartz & Stratton (1993) found that a six-month endurance training programme significantly improved early diastolic filling in younger and older healthy, male subjects. This is in contrast to the findings in the present study to date. There are a number of possible explanations for this. Firstly their subjects were healthy with no evidence of any cardiovascular disease or modifiable risk factors for cardiovascular disease (smoking, hypertension, etc.). It has already been noted that cardiac disease, risk factors for cardiac disease and aging are predictors of diastolic dysfunction, and indeed the older men in the study by Levy, Cerqueira, Abrass, Schwartz & Stratton (1993) did have reduced early diastolic filling. The fact that both the older and younger subjects in their study improved diastolic function whereas those in the present study did not could be due to their absence of cardiac disease or risk factors for cardiac disease.

Secondly it could be due to the longer training period. Thirdly it could be due to changes in body composition (weight loss, reduced fat mass, etc) over the six month training period, which were not reported, but six months of training certainly has the potential to produce significant weight loss or loss of fat mass. Fischer et al (2003) demonstrated that high body mass index was associated with impaired left ventricular function. In the present study there was no weight loss in the exercise group post training possibly due to the short training period. It is possible that the lack of weight loss may have contributed to the lack of improvement in diastolic function, as most patients were overweight (BMI 25-30) or obese (BMI >30).

However, the factor most likely to explain the difference between the two trial results is that in the study by Levy, Cerqueira, Abrass, Schwartz & Stratton (1993) both younger and older subjects significantly reduced their heart rates post training, thereby lengthening diastole, whereas those in the present study did not.

Petrella, Cunningham & Paterson (1997) found that a five day, intensive training programme significantly increased left ventricular diastolic function. E-wave velocity increased (69.3m/s, SD +/-9.4 to 71.2m/s, SD +/-6.6), A-wave velocity decreased (69.9m/s, SD +/-14.5 to 59.2m/s, SD +/-13.5), E/A ratio increased (0.94, SD +/-0.22 to 1.21, SD +/-0.04) and IVRT decreased (95ms, SD +/-18 to 72ms, SD +/-8) ($p < 0.05$ in all cases). After 21 days of detraining these figures returned to near baseline figures ($p < 0.05$ in all cases). Changes in heart rate were minimal, probably due to the very short training period, and unlikely to explain the changes in diastolic function (pre-training 71, SD +/-12, post-training 67, SD +/-11, detraining 69, SD +/-9). Again the differences in the findings of this study and the present study could be due to the fact that Petrella, Cunningham & Paterson (1997) used healthy subjects with no evidence of cardiac disease or risk factors for cardiac disease. It is also possible that the high intensity of training used by Petrella, Cunningham & Paterson (1997) compared to the more moderate intensity training used in the present study had some influence.

The effects of exercise training on diastolic function in patients with cardiovascular disease have received little study. A number of authors have reported that exercise

training in such patients has no deleterious effect on left ventricular diastolic function or dimensions. Dubach et al (1997) reported that patients with reduced systolic function following myocardial infarction (mean ejection fraction 32.3 +/- 6%) who underwent a two month residential exercise programme showed no significant differences in left ventricular systolic function or diastolic dimensions, despite a significant improvement in exercise capacity. A follow up report (Myers et al 2000) confirmed that the improvement in exercise capacity persisted and there were still no changes in left ventricular systolic function or diastolic dimensions. Trans-mitral flow patterns were not reported so direct comparison with the present study is therefore not possible. However, improvement in diastolic function should result in increased end diastolic volume and this was not seen in their study either at the time of the initial report (Dubach et al, 1997) or at one year follow up (Myers et al, 2000).

The present study, to date, has also shown no improvement in diastolic function. This suggests that exercise in patients with myocardial damage may not improve diastolic function.

However, this suggestion is challenged by the results of the study by Yu et al (2004). They found that, compared to a control group, an eight-week programme of exercise in patients with recent myocardial infarction or elective percutaneous coronary intervention, significantly improved markers of diastolic function, especially in a sub-group of patients with an abnormal relaxation pattern (defined as E/A ratio <1, or E/A ratio 1-2 with E-wave deceleration time >240ms). There was no improvement in

ejection fraction.

This is the converse of the finding to date in the present study, where there has been a significant improvement in ejection fraction and no change in diastolic function. This difference is difficult to explain, especially as the training regime in both studies was very similar in intensity and duration. There are some differences in the subjects in each study. The present study has only included patients with some myocardial damage (follow myocardial infarction or troponin positive acute coronary syndrome) *and* some degree of systolic dysfunction. The study by Yu et al (2004) also include patients following elective percutaneous coronary intervention (presumably without myocardial damage), and the mean ejection fraction was normal ($>55\%$) although some patients did have reduced ejection fraction (mean ejection fraction at baseline in the exercise group $57.3 \pm 14.7\%$). However, the inclusion of percutaneous coronary intervention patients does not explain the differences in findings. When the subjects in the study by Yu et al (2004) are stratified into myocardial infarction (71%) and percutaneous coronary intervention (29%) subgroups, only the myocardial infarction subgroup demonstrated improvements in diastolic function.

The most likely explanation is that the subjects in the exercise group in the study by Yu et al (2004) show a greater degree of 'slow relaxation pattern' than the subjects in the present study (mean E-wave velocity 0.60m/s vs 0.92m/s; E/A ratio 0.91 vs 1.28; IVRT 126ms vs 97.7ms). If diastolic function is more impaired at baseline there may be greater potential for improvement, whereas if diastolic function is close to normal

there is little potential for improvement. This could explain the differences in findings for the diastolic function parameters between the two studies.

Similarly since the mean ejection fraction in the exercise group at baseline in the study by Yu et al (2004) was within the normal range (mean 57.3%) there may have been little scope for improvement. The median ejection fraction in the present study's exercise group at baseline was low (43%, interquartile range 34.1 – 48.4) offering a greater potential for improvement.

The implication is that exercise training may have the potential to 'normalize' abnormal parameters of left ventricular function, but this will of course require further study.

What is not yet clear is that, if the improvement in systolic function seen in the present study was, at least in part, due to recruitment of hibernating myocardium, why has this not also produced some improvement in diastolic function? As diastolic function is an energy-requiring rather than passive function it is reasonable to expect that recruitment of hibernating myocardium should also improve diastolic function. Further study using imaging modalities supplemental to echocardiography, such as positron emission tomography, may help to elucidate more information (Barrington et al, 2004).

Limitations

The most obvious limitation of this study is the small sample size, especially at the time of this interim report. The findings to date could easily be increased, reduced or even eliminated when recruitment is complete. Even when recruitment is complete this is still a small scale study.

Another potential weakness is that the two groups were self selecting rather than randomized. As factors other than exercise can affect left ventricular function it is possible that there were significant differences between the two groups other than the amount of exercise they performed. For example, exercise has been shown to reduce peripheral vascular resistance, thereby increasing left ventricular stroke volume (Hambrecht et al, 2000a) and to increase coronary artery flow reserve (Hambrecht et al, 2000b). However, factors other than exercise can also affect these functions, such as smoking and hypertension. As these factors were not recorded in this study it is possible that the control group, consisting of people who declined the cardiac rehabilitation course, had less interest in their health and contained a higher proportion of smokers than the exercise group, or failed to take their medication regularly and had higher blood pressure. These factors could then account for the failure of the control group to increase their ejection fraction as much as the exercise group.

This study was designed to evaluate the effects of the authors current cardiac rehabilitation programme on left ventricular function. It therefore used an exercise programme designed for patients recovering from myocardial infarction, acute coronary syndrome or revascularization procedures, rather than a programme designed specifically for heart failure. It is possible that a different exercise programme would have a different effect on left ventricular function. Therefore, although it provides evidence on the effect of this type of exercise programme, further research using different exercise programmes will be required before the optimum exercise strategy for patients with impaired left ventricular function can be determined.

This study did not include patients showing diastolic dysfunction with preserved systolic function, so the results cannot be generalized to that patient group.

Recommendations

The often cited recommendation, that the research is repeated with a larger sample size, would, in this case, probably be neither practical nor useful. The aim of this research is to provide evidence to facilitate the development of specific, scientifically based heart failure rehabilitation programmes. As existing cardiac rehabilitation centres around the country tend to differ in the exercise they provide (usually as a result of available resources) the cardiac rehabilitation community already has the

potential to compare the effects of differing exercise programmes on left ventricular function. Thus, if this research was repeated by as many cardiac rehabilitation centres as possible, albeit at a small scale, this might provide some insight as to the most effective type of exercise programme in terms of intensity, frequency, duration, etc. Multiple studies may also allow for meta-analyses of similar programmes to strengthen the significance of the data.

If larger scale studies were to be conducted it would be useful if they contained data on changes in body composition, peripheral vascular resistance, coronary flow reserve and myocardial perfusion imaging (or positron emission tomography if available), as well as the echocardiographic data, in order that the exact mechanisms by which exercise improves left ventricular function (if that is the case) can be determined. It would also be useful if patients with diastolic dysfunction but preserved systolic function could be included and subjected to sub-group analysis (if whole group matching parameters are maintained in the sub-groups) or even studied separately.

Finally long term follow up of patients included in future studies is needed to determine the effects on morbidity and mortality of patients treated conservatively with exercise and medical treatment, rather than with revascularization.

Summary

The effects of exercise on left ventricular function have been subjected to extensive research. However, the results of these studies have often produced conflicting results. This is most likely due to the diversity of subjects studied, ranging from lifelong endurance athletes to obese patients with coronary disease, and the wide range of exercise programmes in terms of intensity, frequency and duration of training.

The interim results of the present small scale study indicate that six weeks of moderate exercise training in patients with reduced left ventricular systolic function following myocardial infarction or troponin positive acute coronary syndrome does produce a significant improvement in systolic function with no effect on diastolic function.

The precise mechanisms by which this systolic improvement is mediated, the reasons for the neutral effect on diastolic function and the optimum exercise strategy for these patients, and the long term effects on morbidity and mortality remain unclear and worthy of further research.

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Glossary

Afterload – the resistance to the outflow of blood from the left ventricle.

Angiotensin converting enzyme inhibitors – a group of drugs which reduce the formation of angiotensin-II, a potent vasoconstrictor which increases peripheral vascular resistance. They have been shown to reduce morbidity and mortality in heart failure.

Acute coronary syndrome – an acute ischaemic insult to a section of myocardium as a result of a blood clot forming in the coronary artery supplying that section. Differs from myocardial infarction in that it does not produce changes on the ECG, suggesting that damage is more minimal.

Beta-blockers – a group of drugs which reduce stimulation of the beta-1 receptors on the heart, thereby slowing heart rate and force of contraction. They have been shown to reduce morbidity and mortality in heart failure.

Cardiomyopathy – a family of diseases of the myocardium resulting in impaired function.

Coronary heart disease – disease of the coronary arteries, resulting in the limitation of blood flow through them.

Diastole – the phase of the cardiac cycle during which the ventricles fill with blood from the atria.

Diastolic dysfunction – impaired relaxation and filling of the left ventricle.

Dobutamine stress echocardiography – echocardiography carried out during an infusion of Dobutamine, a powerful inotropic agent which increase rate and force of cardiac contraction and causes vasodilatation. Helps to localize and quantify the extent of myocardial ischaemia and evaluate the potential benefits of revascularization techniques.

Echocardiography – the use of ultrasound to examine the structure and function of the heart.

Ejection fraction – the percentage of blood in the left ventricle at the end of diastole that is ejected during systole.

Endothelial function – the ability of the lining of the blood vessels to produce substances, such as nitric oxide, that cause vasodilatation.

Exercise tolerance test – a test used to detect ischaemic heart disease which involves monitoring the patients ECG during incremental exercise on either a treadmill or static bike.

Heart failure – reduced function of the left ventricle resulting in decreased cardiac output, often associated with symptoms of reduced exercise capacity and breathlessness.

Hypertension – high blood pressure.

Ischaemia – inadequate blood supply to an area of tissue.

Isovolumetric relaxation time – the time from the point in the cardiac cycle when outflow from the left ventricle ceases and the aortic valve closes until the mitral valve opens. During this time the left ventricle begins to relax but there is no change in left ventricular volume.

Left ventricular dysfunction – see **systolic dysfunction** and **diastolic dysfunction**.

Left ventricular hypertrophy – enlargement of the left ventricle which eventually has a detrimental effect on left ventricular function.

Mitral valve – the one-way valve between the left atrium and left ventricle which, if working normally, prevents backflow of blood from the ventricle into the atrium.

Myocardial infarction – death of a section of heart muscle (myocardium) as a result of a blood clot forming in the coronary artery supplying that section.

Myocardial perfusion imaging - an imaging modality that uses radioisotopes (thallium or technetium⁹⁹) to demonstrate tissue perfusion.

Percutaneous coronary intervention – otherwise known as percutaneous transcoronary angioplasty or PTCA. It involves using a balloon catheter to dilate a narrowed section of coronary artery.

Peripheral vascular resistance – the ability of the peripheral blood vessels to relax or contract, thereby varying the resistance to the flow of blood and controlling blood pressure.

Positron emission tomography (PET) – an imaging modality that uses short lived positron-emitting radionuclides to demonstrate tissue perfusion or viability through changes in substrate metabolism secondary to ischaemia.

Spironolactone – a potassium sparing diuretic which has been shown to reduce mortality in heart failure.

Systole – the phase of the cardiac cycle during which the ventricles contract.

Systolic dysfunction – impaired contraction and emptying of the left ventricle.

Troponin I – a muscle protein in the myocardium which is released into the blood stream when myocardium is damaged. Blood tests are very sensitive and can detect minimal amounts of troponin I.

Valvular heart disease – disruption of normal intra-cardiac blood flow caused by malfunction of one or more of the heart valves (failure to open and/or close properly).

Ventricular remodeling – change in size (enlargement) and shape of the left ventricle which has a detrimental effect on ventricular function.

Appendices

Appendix 1 - Patient Information Sheet

Appendix 2 - Consent Form

Appendix 3 - Data Collection Form

Appendix 4 – SPSS Output Tables

Appendix 1 - Patient Information Sheet

Research Project to Assess the Effects of Exercise on the Function of the Heart

I would like to invite you to take part in a research project to look at the effects of an exercise programme on the function of the heart. This project has been approved by our Local Research Ethics Committee.

Why have I been chosen?

As part of your routine care you have had an echocardiogram. This was the test that was done when you had to lie on the bed whilst a technician held a special probe covered in jelly against your chest. This displayed the images of your heart on a monitor and the technician then made some measurements to assess the function of your heart.

These measurements indicated that your heart was not working quite as well as it should. This is nothing to be alarmed about. Almost half of all people that have had the same heart problem as you also have a heart which does not work quite as well as it should. This is something that happens naturally as we get older anyway.

The purpose of the research project is to see if an exercise programme improves the hearts function. We already know that exercise is good for you, but we are trying to find out exactly how the exercise has these beneficial effects.

What will I have to do?

Taking part in this research project will simply involve having another echocardiogram about 3 months after you leave hospital. This is the only thing different to your usual care.

What about the exercise?

You will be invited to join the cardiac rehabilitation programme, as is everyone with heart problems like yours. The cardiac rehabilitation programme involves attending the hospital twice weekly for 6 weeks for a course of exercise in a group, education to teach you all about heart problems, and stress management. Most people enjoy these courses and find them very beneficial.

The research project will examine the effects of exercise on the hearts function by repeating the echocardiogram after the 6-week cardiac rehabilitation exercise programme to see if there has been any improvement.

What if I don't want to do the exercise programme?

If you decide you do not wish to take part in this my team and I will still provide you with all the advice and support that you feel you need.

If you decide not to take part in the cardiac rehabilitation programme you could still take part in the research project. This is because we need a group of people who have not done the exercise for comparison. In this case you would just have another echocardiogram about 3 months after you leave hospital.

Is there any risk involved?

None at all. Echocardiograms are completely free of risk as they only use sound waves; it is exactly the same as the test a pregnant lady has to see the baby.

Are there any benefits to taking part?

Not directly for you, but the results of the study should help us to formulate an exercise programme designed specifically to benefit people like your self.

Will the research affect my treatment?

Not at all. Taking part in this study, whether you decide to exercise or not, simply involves having one extra echocardiogram. Whether you take part or not, the research study will have no effect on your normal treatment.

Who will see the results?

The results of the echocardiogram will go to your consultant at the hospital, as normal. When the results of the research are published, either locally amongst the medical community or in a medical journal, there will be no information included which could identify you. You will be completely anonymous.

Do I have to take part?

You are free to decide whether you want to take part or not. Please take a couple of days to think about it if you need to. If you want to ask any questions please ask the ward staff to contact me on bleep 138.

Thank you.

[Name] BSc(Hons), RN
Senior Cardiac Rehabilitation Nurse

Appendix 2 - Consent Form

Research Project to Assess the Effects of Exercise on the Function of the Heart

Patient label

I confirm that I have fully explained the purpose and nature of this study to the above named patient

Researcher: Print Name _____

Signature _____

I agree that the purpose and nature of this study have been fully explained to me by the researcher. I have been given a written information sheet and have had sufficient time to decide whether or not I wish to participate in this study.

I understand that this research will not affect my treatment in any way, and that by agreeing to participate I will only be subject to one additional echocardiogram.

I also understand that I am free to withdraw from the research at any time.

Patient: Print Name _____

Signature _____

Appendix 3 - Data Collection Form

Patient label

Exercise group / Control group
(Delete as appropriate)

Variable	First echocardiogram	Second echocardiogram
Heart rate		
Ejection fraction		
Isovolumetric relaxation time		
E-wave size		
E-wave duration		
E-wave deceleration time		
A wave size		
A wave duration		
E/A ratio		
Valvular regurgitation?		
Medication		

Appendix 4 – SPSS Output Tables

Table 1. Exercise Group Baseline Statistics

		Age	EFpre	IVRTpre	Esizepre	Edurpre	EDTpre	Asizepre	Adurpre	EARpre	HRpre
N	Valid	8	8	8	8	8	8	8	8	8	8
	Missing	0	0	0	0	0	0	0	0	0	0
Mean		58.25	41.475	97.738	.9200	408.025	337.487	.7325	146.000	1.2838	63.25
Median		58.00	43.000	99.800	.9250	407.550	335.900	.6750	135.850	1.2800	59.50
Std. Deviation		10.539	8.1265	31.1923	.27365	127.5860	101.3941	.17178	45.3913	.41600	15.582
Skewness		-.569	-.233	-.181	.225	-.138	-.452	1.202	1.996	1.432	2.321
Std. Error of Skewness		.752	.752	.752	.752	.752	.752	.752	.752	.752	.752
Minimum		40	29.1	49.9	.57	205.0	165.1	.55	103.4	.83	51
Maximum		71	52.6	140.5	1.36	582.3	458.0	1.05	249.5	2.17	100
Percentiles	25	50.00	34.100	72.100	.6400	304.525	259.775	.6200	115.050	.9550	53.75
	50	58.00	43.000	99.800	.9250	407.550	335.900	.6750	135.850	1.2800	59.50
	75	67.75	48.375	124.775	1.1450	532.375	437.575	.8825	153.900	1.3875	63.75

Abbreviations in tables 1, 2, 3, 6 & 7:

EFpre = ejection fraction at baseline (% of volume in left ventricle at end of diastole which is ejected at systole)

IVRTpre = isovolumetric relaxation time at baseline (milliseconds)

Esizepre = E wave size at baseline (peak speed of trans-mitral flow in metres/second in early diastole)

Edurpre = E wave duration at baseline (milliseconds)

EDTpre = E wave deceleration time at baseline (milliseconds)

Asizepre = A wave size at baseline (peak speed of trans-mitral flow in metres/second during atrial contraction)

Adurpre = A wave duration at baseline (milliseconds)

EARpre = E / A ratio at baseline

HRpre = heart rate at baseline

Table 1 shows the median (Interquartile range) and range for age, heart rate and echocardiographic measurements of the subjects in the exercise group at baseline. Median age 58.00 years (50 – 67.5), median heart rate 59.5 (53.75 – 63.75), median ejection fraction 43.0% (34.1 – 48.38).

Table 2. Control Group Baseline Statistics

		Age	EFpre	IVRTpre	Esizepre	Edurpre	EDTpre	Asizepre	Adurpre	EARpre	HRpre
N	Valid	9	9	9	9	9	9	9	9	9	9
	Missing	0	0	0	0	0	0	0	0	0	0
Mean		65.44	44.444	103.500	.8244	358.389	487.056	.9622	129.378	.9644	64.11
Median		70.00	49.500	105.400	.6000	327.200	475.500	.9500	127.500	.8100	65.00
Std. Deviation		8.719	9.3574	17.7126	.36851	86.7189	163.4752	.31072	29.9943	.62448	8.609
Skewness		-.927	-.735	-1.043	.721	1.592	-.076	.796	-.103	1.660	-1.278
Std. Error of Skewness		.717	.717	.717	.717	.717	.717	.717	.717	.717	.717
Minimum		49	29.8	66.5	.47	271.7	197.5	.53	72.1	.36	45
Maximum		75	53.2	127.5	1.42	547.1	760.8	1.59	184.8	2.39	74
Percentiles	25	58.00	33.700	94.250	.5300	304.050	386.750	.7300	116.450	.5100	61.00
	50	70.00	49.500	105.400	.6000	327.200	475.500	.9500	127.500	.8100	65.00
	75	72.00	51.850	114.600	1.2250	403.000	609.650	1.1150	143.250	1.2750	70.50

Table 2 shows the median (Interquartile range) and range for age heart rate and echocardiographic measurements of the subjects in the control group at baseline. Median age 70 years (58 - 72), median heart rate 65 (61 – 70.5), median ejection fraction 49.5% (33.70 – 51.85).

Table 3. Mann-Whitney Test Statistics(b)

	Age	EFpre	IVRTpre	Esizepre	Edurationpre	Eedctimepre	Asizepre	Adurpre	EARpre	HRpre
Mann-Whitney U	19.500	27.000	32.000	29.000	25.000	15.000	15.000	28.500	17.000	22.500
Wilcoxon W	55.500	63.000	68.000	74.000	70.000	51.000	51.000	73.500	62.000	58.500
Z	-1.592	-.866	-.386	-.675	-1.058	-2.021	-2.022	-.725	-1.828	-1.301
Asymp. Sig. (2-tailed)	.111	.386	.699	.500	.290	.043	.043	.469	.068	.193
Exact Sig. [2*(1-tailed Sig.)]	.114(a)	.423(a)	.743(a)	.541(a)	.321(a)	.046(a)	.046(a)	.481(a)	.074(a)	.200(a)

a Not corrected for ties.

b Grouping Variable: Group

Table 3 shows the independent group comparison statistics between the exercise and control groups at baseline. There are no statistically significant differences between the two groups for age, heart rate or ejection fraction (systolic function). Two of the measures of diastolic function, E-wave deceleration time and A-wave size, do appear to be statistically different ($p=0.043$ in both cases). This may be due to the very small sample size and may disappear when recruitment is complete.

Table 4. Details of Values on Repeat Testing (post) in the Exercise Group

		EFpost	IVRTpost	Esizepost	Edurpost	EDTpost	Asizepost	Adurpost	EARpost	HRpost
N	Valid	8	8	8	8	8	8	8	8	8
	Missing	0	0	0	0	0	0	0	0	0
Mean		55.137	84.788	.9738	370.613	373.975	.7688	124.550	1.4200	64.38
Median		58.600	80.400	.9250	354.900	360.050	.7550	138.650	1.1150	64.00
Std. Deviation		13.7584	19.6005	.30071	110.3813	137.7941	.22750	51.9015	.92483	10.322
Skewness		-1.382	.567	.890	.974	.219	.273	-2.498	2.736	.046
Std. Error of Skewness		.752	.752	.752	.752	.752	.752	.752	.752	.752
Minimum		26.1	61.0	.68	216.3	183.5	.42	.0	.88	46
Maximum		71.7	118.3	1.54	591.5	569.2	1.13	160.8	3.69	83
Percentiles	25	49.575	67.900	.6900	307.775	261.675	.6200	124.775	1.0475	60.50
	50	58.600	80.400	.9250	354.900	360.050	.7550	138.650	1.1150	64.00
	75	64.100	99.800	1.1600	422.800	518.325	.9725	153.450	1.2625	68.50

Abbreviations in tables 4, 5, 6 & 7:

EFpost = ejection fraction at repeat testing (% of volume in left ventricle at end of diastole which is ejected at systole)

IVRTpost = isovolumetric relaxation time at repeat testing (milliseconds)

Esizepost = E wave size at repeat testing (peak speed of trans-mitral flow in metres/second in early diastole)

Edurpost = E wave duration at repeat testing (milliseconds)

EDTpost = E wave deceleration time at repeat testing (milliseconds)

Asizepost = A wave size at repeat testing (peak speed of trans-mitral flow in metres/second during atrial contraction)

Adurpost = A wave duration at repeat testing (milliseconds)

EARpost = E / A ratio at repeat testing

HRpost = heart rate at repeat testing

Table 4 shows the median (Interquartile range) and range for heart rate and

echocardiographic measurements of the subjects in the exercise group at repeat measuring

(post exercise course). Median heart rate 64.0 (60.5 – 68.5), median ejection fraction

58.6% (49.58 – 64.1).

Table 5. Details of Values on Repeat Testing (post) in the Control Group

		EFpost	IVRTpost	Esizepost	Edurpost	EDTpost	Asizepost	Adurpost	EARpost	HRpost
N	Valid	9	9	9	9	9	9	9	9	9
	Missing	0	0	0	0	0	0	0	0	0
Mean		51.867	116.256	.7922	341.344	313.267	.9167	154.844	.9224	64.56
Median		52.000	110.900	.7700	332.700	329.200	.8600	149.700	.7200	64.00
Std. Deviation		10.7426	27.1466	.25907	150.4092	108.3292	.32101	32.3497	.37003	10.442
Skewness		.970	.686	.032	.381	-.577	1.490	1.051	.747	.346
Std. Error of Skewness		.717	.717	.717	.717	.717	.717	.717	.717	.717
Minimum		38.7	77.6	.37	122.0	110.5	.51	110.9	.56	48
Maximum		73.8	170.1	1.22	587.8	449.2	1.65	221.8	1.52	82
Percentiles	25	43.600	97.050	.6100	231.050	243.750	.7200	133.100	.6050	58.00
	50	52.000	110.900	.7700	332.700	329.200	.8600	149.700	.7200	64.00
	75	58.350	133.100	.9800	478.750	413.800	1.0200	172.800	1.2900	72.50

Table 5 shows the median (Interquartile range) and range for heart rate and echocardiographic measurements of the subjects in the control group at repeat measuring (approximately 3 months after index event). Median heart rate 64.00 (58 – 72.5), median ejection fraction 52% (43.6 – 58.35).

Table 6. Comparison of pre and post measurements in exercise group (c)**Test Statistics(c)**

	EFpost EFpre	IVRTpost IVRTpre	Esizepost Esizepre	Edurpost Edurpre	Asizepost Asizepre	Adurpost Adurpre	EARpost EARpre	HRpost HRpre
Z	2.240(a)	-1.262(b)	-.700(a)	-.845(b)	-.943(a)	-.280(b)	-.280(a)	.560(a)
Asymp. Sig. (2-tailed)	.025	.207	.484	.398	.345	.779	.779	.575

a Based on negative ranks.

b Based on positive ranks.

c Wilcoxon Signed Ranks Test

Table 6 shows the Wilcoxon Signed Rank Test statistics for pre and post measurements in the exercise group. This shows a statistically significant increase in ejection fraction following the exercise course (median EF pre 43.0%, median EF post 58.6%, Z statistic 2.240, $p=0.025$). This equates to a 36.3% improvement. If this is maintained when recruitment is completed the null hypothesis for this measurement can be rejected. There are no statistically significant differences in heart rate or any measure of diastolic function.

Table 7. Comparison of pre and post measurements in control group (c)**Test Statistics(c)**

	EFpost - EFpre	IVRTpost - IVRTpre	Esizepost - Esizepre	Edurpost - Edurpre	Asizepost - Asizepre	Adurpost - Adurpre	EARpost - EARpre	HRpost - HRpre
Z	-1.481(a)	-1.067(a)	-.296(b)	-.296(b)	-.889(b)	-2.521(a)	-.059(a)	-.140(b)
Asymp. Sig. (2- tailed)	.139	.286	.767	.767	.374	.012	.953	.889

a Based on negative ranks.

b Based on positive ranks.

c Wilcoxon Signed Ranks Test

Table 7 shows the Wilcoxon Signed Rank Test statistics for pre and post measurements in the control group. In contrast to the exercise group there is no significant difference in ejection fraction between measurements in the control group. There does appear to be a statistically significant difference in A wave duration (median A wave duration pre 127.5 milliseconds, median A wave duration post 149.7 milliseconds, Z statistic 2.521, $p=0.012$). There are no statistically significant differences in any of the other measurements of diastolic function or in heart rate.

Table 8. Exercise Group Pre & Post Weights

		Preweight	Postweight
N	Valid	8	8
	Missing	0	0
Mean		78.975	79.013
Median		76.450	77.100
Std. Deviation		13.2150	14.5359
Skewness		.844	.702
Std. Error of Skewness		.752	.752
Minimum		64.0	62.0
Maximum		99.0	101.5
Percentiles	25	68.725	67.050
	50	76.450	77.100
	75	93.700	94.250

Table 8 shows the median values and interquartile range for the exercise group weights pre and post exercise course.

Table 9. Control Group Pre Weight (not re-weighted post)

N	Valid	9
	Missing	0
Mean		84.744
Median		85.500
Std. Deviation		23.8451
Skewness		.337
Std. Error of Skewness		.717
Minimum		50.8
Maximum		124.8
Percentiles	25	65.050
	50	85.500
	75	102.250

Table 9 shows the median values and interquartile range for the control group weights at baseline. This group were not reweighed.

Table 10. Weight comparisons (means).

Group		Pre-weight	Post-weight
exercise	Mean	78.975	79.013
	N	8	8
	Std. Deviation	13.2150	14.5359
control	Mean	84.744	
	N	9	
	Std. Deviation	23.8451	
Total	Mean	82.029	79.013
	N	17	8
	Std. Deviation	19.2226	14.5359

Note: control group patients were not re-weighed

Table 10 shows the mean weights of the exercise and control groups. Note there is a wide standard deviation in the control group.

Table 11. Mann-Whitney Test Statistics(b)

Ranks

	Group	N	Mean Rank	Sum of Ranks
Prewrite	exercise	8	8.50	68.00
	control	9	9.44	85.00
	Total	17		

Test Statistics(b)

	Pre-weight
Mann-Whitney U	32.000
Wilcoxon W	68.000
Z	-.385
Asymp. Sig. (2-tailed)	.700
Exact Sig. [2*(1-tailed Sig.)]	.743(a)

a Not corrected for ties.

b Grouping Variable: Group

Table 11 shows the independent group comparison statistics for weight between the exercise and control groups at baseline. There is no statistically significant difference between the two groups for weight.

Table 12. Exercise Group Wilcoxon Signed Ranks Test

Ranks

		N	Mean Rank	Sum of Ranks
Postweight - Preweight	Negative Ranks	4(a)	3.25	13.00
	Positive Ranks	3(b)	5.00	15.00
	Ties	1(c)		
	Total	8		

a Postweight < Preweight

b Postweight > Preweight

c Postweight = Preweight

Test Statistics(b)

	Postweight - Preweight
Z	-.170(a)
Asymp. Sig. (2-tailed)	.865

a Based on negative ranks.

b Wilcoxon Signed Ranks Test

Table 10 shows the within group comparison statistic for weight before and after the exercise programme. There is no significant change in weight.

Table 13. Exercise Group Wilcoxon Signed Ranks Test**Statistics**

		LVEDVpre	LVEDVpost
N	Valid	8	8
	Missing	0	0
Median		136.750	144.050
Minimum		105.2	106.1
Maximum		168.0	177.3
Percentiles	25	134.500	131.725
	50	136.750	144.050
	75	157.100	158.300

Descriptive Statistics

	N	Percentiles		
		25th	50th (Median)	75th
LVEDVpre	8	134.500	136.750	157.100
LVEDVpost	8	131.725	144.050	158.300

Test Statistics(b)

	LVEDVpost - LVEDVpre
Z	-.280(a)
Asymp. Sig. (2-tailed)	.779

a. Based on negative ranks.

b. Wilcoxon Signed Ranks Test

Table 13 shows the within group comparison statistic for left ventricular end-diastolic volume before and after the exercise programme. There is no significant change in volume.